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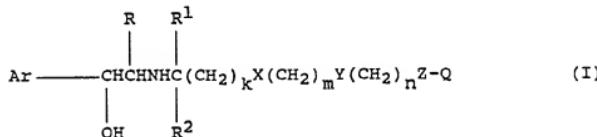
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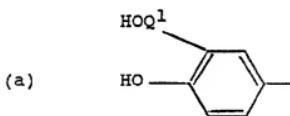
(54) Phenethanolamine derivatives.

(57) The invention provides compounds of the general formula (I)

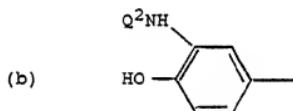


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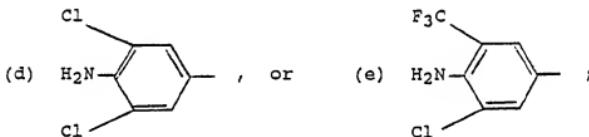
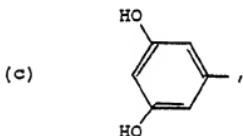
and physiologically acceptable salts and solvates thereof, wherein
Ar represents the group



where Q¹ represents a straight or branched C₁-3alkylene group,



where Q² represents a group R³CO-, R³NHCO-, R³R⁴NSO₂- or R⁵SO₂-, where R³ and R⁴ each represent a hydrogen atom or a C₁-3alkyl group, and R⁵ represents a C₁-3alkyl group,



R represents a hydrogen atom or a C₁-3alkyl group;

R¹ and R² each independently represent a hydrogen atom or a methyl or ethyl group; and k represents an integer from 1 to 8;

m represents zero or an integer from 2 to 7, and;

n represents an integer from 1 to 7 with the proviso that the sum total of k, m and n is 4 to 12;

X represents an oxygen or sulphur atom, and;

Y and Z each represent a bond, or an oxygen or sulphur atom with the proviso that when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7, or when Y and Z each independently represent an oxygen or sulphur atom then n is an integer from 2 to 7;

Q represents a naphthalenyl group which may optionally be substituted by one or two groups selected from C₁-3alkyl, C₁-4alkoxy, hydroxy and halogen.

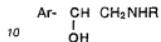
The compounds have a stimulant action at β_2 -adrenoreceptors and may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

PHENETHANOLAMINE DERIVATIVES

The compounds have a stimulant action at β_2 -adrenoceptors and may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

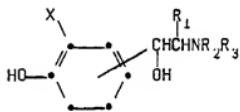
This invention relates to phenethanolamine derivatives having a stimulant action at β_2 -adrenoceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Phenethanolamine derivatives of the general formula



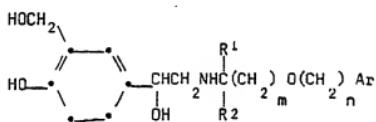
in which Ar represents groupings of the type described hereinafter, and R represents *inter alia* an alkyl, aralkyl, aryloxyalkyl or an optionally substituted phenylalkyloxyalkyl group have previously been described as bronchodilators having stimulant activity at β -adrenoceptors.

15 Thus, for example, British Patent Specification No. 1200886 describes phenethanolamine compounds of the general structure



25 in which X represents *inter alia* a hydroxyC1-6 alkyl group; R1 represents a hydrogen atom or an optionally branched C1-6 alkyl group; R2 represents *inter alia* a hydrogen atom; and R3 represents a hydrogen atom or an optionally branched C1-6 alkyl group, optionally substituted by hydroxyl or amino groups or heterocyclic rings, or R3 represents a cycloalkyl, aralkyl or aryloxyalkyl group, optionally substituted by one or more alkoxy or hydroxyl groups.

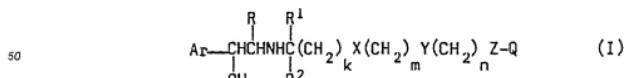
30 UK Patent Specification No. 2140800 describes phenethanolamine compounds of the general structure



40 in which R1 and R2 each represent hydrogen or C1-3 alkyl; m is an integer from 2 to 8; n is an integer from 1 to 7; and Ar represents an optionally substituted phenyl ring.

We have now found a novel group of phenethanolamine derivatives which differ in structure from those described previously (for example, British and UK Patent Specification Nos. 1200886 and 2140800), and have a desirable and potentially useful profile of activity.

45 Thus the present invention provides compounds of the general formula (I)

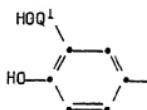


and physiologically acceptable salts and solvates (e.g. hydrates) thereof, which

Ar represents the group

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(a)

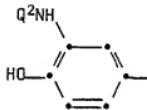


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(where Q¹ represents a straight or branched C₁-₃ alkylene group),

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(b)

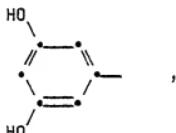


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(where Q² represents a group R³CO-, R³NHCO-, R³R⁴NSO₂- or R⁵SO₂-, where R³ and R⁴ each represent a hydrogen atom or a C₁-₃ alkyl group, and R⁵ represents a C₁-₃ alkyl group),

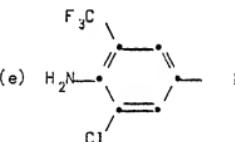
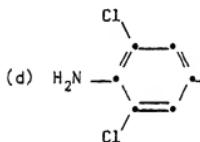
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(c)



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R represents a hydrogen atom or a C₁-₃ alkyl group;
 R' and R⁴ each independently represent a hydrogen atom or a methyl or ethyl group; and
 k represents an integer from 1 to 8;
 45 m represents zero or an integer from 2 to 7, and;
 n represents an integer from 1 to 7 with the proviso that the sum total of k, m and n is 4 to 12;
 X represents an oxygen or sulphur atom, and;
 Y and Z each represent a bond, or an oxygen or sulphur atom with the proviso that when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7, or when Y and Z each 50 independently represent an oxygen or sulphur atom then n is an integer from 2 to 7;
 Q represents a naphthalenyl group which may optionally be substituted by one or two groups selected from C-₁-₄ alkyl, C₁-₄ alkoxy, hydroxy and halogen.

It will be appreciated that the compounds of general formula (I) possess one or more asymmetric carbon atoms. The compounds according to the invention thus include all enantiomers, diastereoisomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the -CH(OH)- group is in the R configuration are preferred.

In the general formula (I), the chain -(CH₂)_k- may be for example a bond, -CH₂- , -(CH₂)₂- , -(CH₂)₃- , -(CH₂)₄- , -(CH₂)₅- or -(CH₂)₇- . The chains

$-(CH_2)_m-$ and $-(CH_2)_n-$

may be for example $-(\text{CH}_2)_2$, $-(\text{CH}_2)_3$, $-(\text{CH}_2)_4$, $-(\text{CH}_2)_5$ or $-(\text{CH}_2)_6$ or the chain $-(\text{CH}_2)_m$ may be a bond.

Preferably the total number of carbon atoms in the chains $-(\text{CH}_2)_x$, $-(\text{CH}_2)_m$ and $-(\text{CH}_2)_n$ is 6 to 12 inclusive. Compounds wherein the sum total of carbon atoms in the chains $-(\text{CH}_2)_x$, $-(\text{CH}_2)_m$ and $-(\text{CH}_2)_n$ is 6, 7, 8, 9, 10 or 11 are particularly preferred.

Examples of compounds of general formula (I) are those wherein X represents an oxygen or sulphur atom and Y and Z each represent a bond. Further examples are those wherein X represents an oxygen or sulphur atom, Y represents a bond and Z represents an oxygen or sulphur atom. Still further examples of compounds of general formula (I) are those wherein X, Y and Z each represent oxygen or sulphur atoms.

A preferred group of compounds of general formula (I) are those in which X is an oxygen atom. Within this group of compounds Y preferably represents a bond or an oxygen atom and Z represents a bond or an oxygen or sulphur atom.

Preferred compounds from within this group are those wherein X is an oxygen atom, Y is a bond and Z is a bond, or X is an oxygen atom, Y is a bond and Z is an oxygen or sulphur atom.

In the compounds of formula (I) R may be, for example, a methyl, ethyl, propyl or isopropyl group. R, R¹ and R² are each preferably a hydrogen atom or a methyl group.

Another preferred group of compounds are those wherein R^1 and R^2 are both hydrogen atoms, or R^1 is

Another preferred group of compounds are those wherein R¹ is a hydrogen atom and R² is a C₁-₃ alkyl group, particularly a methyl group, or R¹ is a methyl group and R² is a methyl group.

In the compounds of formula (I), Q¹ may be, for example, -CH₂-, -CH(CH₃)-, -(CH₂)₂- or -(CH₂)₃-.

^{2b} Q^2 may represent for example HCO^- , CH_3CO^- , H_2NCO^- , $(CH_3)_2NSO_2^-$ or $CH_3SO_2^-$. Q^2 preferably represents HCO^- or, more particularly, $CH_3SO_2^-$.

The group Q is attached to the rest of the molecule through any available position on the naphthalenyl moiety. Any substituent(s) in the group Q may be attached to either the same or different rings of the naphthalenyl moiety. When the group Q is substituted by one or two halogen atoms, these may be chlorine, fluorine or bromine.

A preferred group of compounds of general formula (I) are those wherein Q is an unsubstituted naphthalenyl moiety attached to the remainder of the molecule at the 1- or 2- position.

A further group of preferred compounds of formula (I) are those in which the group Q is substituted by a single substituent, for example, a methoxy group.

35 In one preferred group of compounds of general formula (I) Ar represents group (a) wherein Q¹ represents -CH₂-; or group (b) wherein Q² represents CH₃SO₂-; or group (c) or group (d); R represents a hydrogen atom; R¹ represents a hydrogen atom or a methyl group; R² represents a hydrogen atom; X represents an oxygen atom; Y represents a bond; Z represents a bond or an oxygen or sulphur atom; and k is 5, m is zero and n is an integer from 1 to 4.

Preferred compounds according to the invention are 4-hydroxy- α' -[[[6-[2-(naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedi(methanol).

4-amino-3,5-dichloro- α -[[6-[3-(6-methoxy-2-naphthalenyl)propoxy]hexyl]amino]methyl]benzenemethanol,

5-[1-hydroxy-2-[[6-[(2-naphthalenyl)ethoxy]hexyl]amino]ethyl]-1,3-benzenediol

N-[2-hydroxy-5-[1-hydroxy-2-[[6-[4-[(2-naphthalenyl)oxy]butoxy]hexyl]amino]ethyl]phenyl]-

methanesulphonamide, and 4-hydroxy-a¹-[[6-[2-(1-naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol, and their physiologically acceptable salts and solvates.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxybenzoates, 2- or 4-hydroxybenzoates, 4-chlorobenzoates, benzenesulphonates, p-toluenesulphonates, naphthalenesulphonates, methanesulphonates, sulphamates, ascorbates, salicylates, acetates, diphenylacetates, triphenylacetates, adipates, fumarates, succinates, lactates, glutarates, gluconates, tricarballylates, hydroxynaphthalene carboxylates e.g. 1-hydroxy- or 3-hydroxy-2-naphthalene carboxylates, or oleates. The compounds may also form salts with suitable bases where appropriate. Examples of such salts are alkali metal (e.g. sodium and potassium) and alkaline earth metal (e.g. calcium or magnesium) salts, and salts with organic bases (e.g. triethylamine).

The compounds according to the invention have a stimulant action at β_2 -adrenoceptors, which furthermore is of a particularly advantageous profile. The stimulant action was demonstrated in the isolated

trachea of the guinea-pig, where compounds were shown to cause relaxation of contractions induced by PGF_{2α} or electrical stimulation. A prolonged duration of action has also been observed.

The compounds according to the invention may be used in the treatment of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis.

5 The compounds according to the invention are also indicated as useful for the treatment of inflammatory and allergic skin diseases, congestive heart failure, depression, premature labour, glaucoma, and in the treatment of conditions in which there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

10 The invention accordingly further provides compounds of formula (I) and their physiologically acceptable salts and solvates for use in the therapy or prophylaxis of diseases associated with reversible airways obstruction in human or animal subjects.

15 The compounds according to the invention may be formulated for administration in any convenient way. The invention therefore includes within its scope pharmaceutical compositions comprising at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof formulated for use in human or veterinary medicine. Such compositions may be presented for use with physiologically acceptable carriers or excipients, optionally with supplementary medicinal agents.

20 The compounds may be formulated in a form suitable for administration by inhalation or insufflation, or for oral, buccal, parenteral, topical (including nasal) or rectal administration. Administration by inhalation or insufflation is preferred.

25 For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlortetrafluoroethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

30 Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in for example capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

35 For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For buccal administration the composition may take the form of tablets, drops or lozenges formulated in conventional manner.

40 The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

45 For topical administration the pharmaceutical composition may take the form of ointments, lotions or creams formulated in a conventional manner, with for example an aqueous or oily base, generally with the addition of suitable thickening agents and/or solvents. For nasal application, the composition may take the form of a spray, formulated for example as an aqueous solution or suspension or as an aerosol with the use of a suitable propellant.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

50 Where pharmaceutical compositions are described above for oral, buccal, rectal or topical administration, these may be presented in a conventional manner associated with controlled release forms.

55 A proposed daily dosage of active compound for the treatment of man is 0.005mg to 100mg, which may be conveniently administered in one or two doses. The precise dose employed will of course depend on the age and condition of the patient and on the route of administration. Thus a suitable dose for administration by inhalation is 0.005mg to 20mg, for oral administration is 0.02mg to 100mg, and for parenteral administration is 0.01mg to 2mg for administration by bolus injection and 0.01mg to 25mg for administration by infusion.

The compounds according to the invention may be prepared by a number of processes. In the following description, Ar, k, m, n, X, Y, Z, Q, R, R¹ and R² are as defined for general formula (I) unless otherwise

specified. In the preparation of both intermediates and end-products the final step in the reaction may be the removal of a protecting group. Suitable protecting groups and their removal are described in general process (3) below.

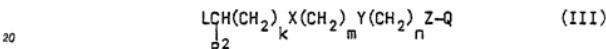
In one general process (1), a compound of general formula (I) may be prepared by alkylation.
 5 Conventional alkylation procedures may be used.

Thus, for example, in one process (a), a compound of general formula (I) in which R¹ is a hydrogen atom may be prepared by alkylation of an amine of general formula (II)



15 (wherein R⁶ is a hydrogen atom or a protecting group and R' is a hydrogen atom) followed by removal of any protecting group where present.

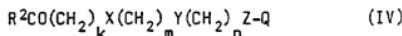
The alkylation (a) may be effected using an alkylating agent of general formula (III):



(wherein L is a leaving group, for example a halogen atom such as chlorine, bromine or iodine; or a hydrocarbysulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy).

25 The alkylation is preferably effected in the presence of a suitable acid scavenger, for example, inorganic bases such as sodium or potassium carbonate, organic bases such as triethylamine, diisopropylethylamine or pyridine, or alkylene oxides such as ethylene oxide or propylene oxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, a substituted amide e.g. dimethylformamide or a chlorinated hydrocarbon e.g. chloroform, at a temperature between ambient and the reflux temperature of the solvent.

30 According to another example (b) of an alkylation process, a compound of general formula (I) in which R¹ represents a hydrogen atom may be prepared by alkylation of an amine of general formula (II), as previously defined except that R' is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (IV):



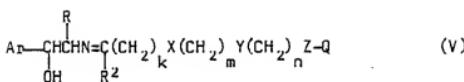
40 in the presence of a reducing agent, followed when necessary by removal of any protecting groups.

Examples of suitable R' groups convertible into a hydrogen atom are arylmethyl groups such as benzyl, α -methylbenzyl and benzhydryl.

45 Suitable reducing agents include hydrogen in the presence of a catalyst such as platinum, platinum oxide, palladium, palladium oxide, Raney nickel or rhodium, on a support such as charcoal, using an alcohol, e.g. ethanol or methanol, or an ester e.g. ethyl acetate, or an ether e.g. tetrahydrofuran, or water, as reaction solvent, or a mixture of solvents, e.g. a mixture of two or more of those just described, at normal or elevated temperature and pressure, for example from 20 to 100 °C and from 1 to 10 atmospheres.

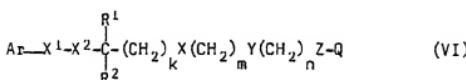
50 Alternatively when one or both of R⁶ and R' are hydrogen atoms, the reducing agent may be a hydride such as diborane or a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride. Suitable solvents for the reaction with these reducing agents will depend on the particular hydride used, but will include alcohols such as methanol or ethanol, or ethers such as diethyl ether or tert-butyl methyl ether, or tetrahydrofuran.

When a compound of formula (II) where R⁶ and R' are each hydrogen atoms is used, the intermediate 55 imine of formula (V) may be formed:



Reduction of the imine using the conditions described above, followed, where necessary, by removal of any protecting groups, gives compound of general formula (I).

10 In another general process (2) compounds of formula (I) may be prepared by reducing an intermediate of general formula (VI):



wherein at least one of X^1 and X^2 represents a reducible group and the other(s) take the appropriate meaning as follows, which is X^1 is $-\text{CH}(\text{OH})-$ and X^2 is $-\text{CHNR}^6-$ (where R^6 represents a hydrogen atom or a protecting group), followed where necessary by removal of any protecting groups.

20 Suitable reducible groups include those wherein X^1 is a group >C=O and X^2 is a group $-\text{CHNR}^6-$ (wherein R^1 represents a group convertible to hydrogen by catalytic hydrogenation, for example an arylmethyl group such as benzyl, benzhydryl or α -methylbenzyl).

The reduction may be effected using reducing agents conveniently employed for the reduction of ketones or protected amines.

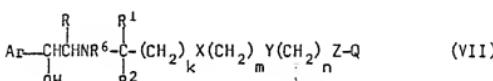
25 Thus, for example, when X^1 in general formula (VI) represents a >C=O group this may be reduced to a $-\text{CH}(\text{OH})-$ group using hydrogen in the presence of a catalyst such as platinum, platinum oxide, palladium, palladium oxide, Raney nickel or rhodium, on a support such as charcoal, using an alcohol e.g. ethanol, an ester e.g. ethyl acetate, an ether e.g. tetrahydrofuran, or water, as reaction solvent, or a mixture of solvents, e.g. a mixture of two or more of those just described, at normal or elevated temperature and pressure, for example from 20 to 100 °C and from 1 to 10 atmospheres. Alternatively, the reducing agent may be, for example, a hydride such as diborane or a metal hydride such as lithium aluminium hydride, sodium bis(2-methoxyethoxy) aluminium hydride, sodium borohydride or aluminium hydride. The reaction may be effected in an appropriate solvent, such as an alcohol e.g. methanol or ethanol, or an ether such as tetrahydrofuran, or a halogenated hydrocarbon such as dichloromethane.

30 When X^2 in general formula (VI) represents a $-\text{CHNR}^6-$ group this may be reduced to a $-\text{CHRNH}-$ group using hydrogen in the presence of a catalyst as described above.

Where it is desired to use a protected intermediate of general formula (VI) it is particularly convenient to use a protecting group R^6 which is capable of being removed under the reducing conditions, for example hydrogen and a catalyst, thus avoiding the need for a separate deprotection step. Suitable protecting groups of this type include arylmethyl groups such as benzyl, benzhydryl and α -methylbenzyl.

40 In the above reduction process, and also in the preparation of intermediates, care must be taken when using a hydride reducing agent and end-products are required in which Q^2 represents the group R^3CO^- .

In a further process (3) compounds of formula (I) may be prepared by deprotecting an intermediate of general formula (VII)



50 wherein R^6 is a protecting group, and/or at least one of the hydroxy group(s) in Ar is protected, and/or the group Q contains a protecting group.

The protecting group may be any conventional protecting group as described for example in "Protective Groups in Organic Synthesis", by Theodora Greene (John Wiley and Sons Inc, 1981). Thus, for example, hydroxyl groups may be protected by arylmethyl groups such as benzyl, diphenylmethyl or triphenylmethyl, by acyl groups such as acetyl, or as tetrahydropyranyl derivatives. Examples of suitable amino protecting groups include arylmethyl groups such as benzyl, α -methylbenzyl, diphenylmethyl or

triphenylmethyl, and acyl groups such as acetyl, trichloroacetyl or trifluoroacetyl.

The deprotection to yield a compound of general formula (I) may be effected using conventional techniques. Thus for example arylmethyl groups may be removed by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal). Tetrahydropyranyl groups may be cleaved by hydrolysis under acidic conditions. Acyl groups may be removed by hydrolysis with an acid such as a mineral acid e.g. hydrochloric acid, or a base such as sodium hydroxide or potassium carbonate, and a group such as trichloroacetyl may be removed by reduction with, for example, zinc and acetic acid.

Intermediates of formula (VI) for use in the reduction process (2) in which X^1 is the group >C=O may be prepared by reaction of a haloketone of formula (VIII)

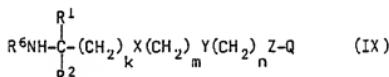
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(wherein Hal represents a halogen atom e.g. bromine) with an amine of formula (IX)

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(wherein R^6 is a hydrogen atom or a group convertible thereto by catalytic hydrogenation).

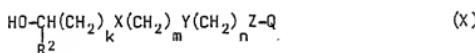
The reaction may be effected in a cold or hot solvent, for example tetrahydrofuran, tert-butyl methyl ether, dioxan, chloroform, dichloromethane, dimethylformamide, acetonitrile, a ketone such as butanone or methylisobutylketone, or an ester such as ethyl acetate, preferably in the presence of a base such as diisopropylethylamine, sodium carbonate or other acid scavenger such as propylene oxide.

Intermediates of general formula (VI) in which X^1 is the group >C=O may be reduced to the corresponding intermediate in which X^1 is the group -CH(OH)- using for example a metal hydride such as sodium borohydride in a solvent e.g. ethanol, methanol and/or tetrahydrofuran.

Amines of formula (II) and haloketones of formula (VIII) are either known compounds or may be prepared by methods analogous to those described for the preparation of known compounds.

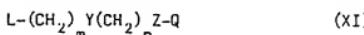
Intermediates of formula (III) may be prepared from the corresponding alcohols of formula (X) using methods capable of effecting the conversion

35



For example compounds of formula (III) where L represents a halogen atom may be prepared by reaction of the compounds of formula (X) with a halogenating agent such as a triphenylphosphine-tetrahalogenomethane adduct (conveniently formed in situ e.g. by the reaction of triphenylphosphine and carbon tetrabromide). The reaction may take place in the presence of a solvent such as a chlorinated hydrocarbon (e.g. dichloromethane) at a temperature range of 0-30°.

45 Alcohol of formula (X) may be prepared by reacting a compound of formula (XI)



50

(where L is as defined above) with a compound of formula (XII)

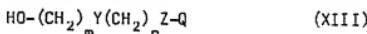
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The reaction may take place optionally in a solvent such as an ether (e.g. tetrahydrofuran or 1,2-dimethoxyethane), an alcohol (e.g. methanol) or an amide (e.g. dimethylformamide) at a temperature up to

the boiling point of the solvent. The reaction may be effected by first generating the anion of the compound of general formula (XII) by adding for example sodium, sodium hydride, potassium hydroxide or sodium hydroxide.

Compounds of formula (XI) may be prepared from the corresponding compounds of formula (XIII)



10 using methods capable of effecting the conversion. For example when L in general formula (XI) represents a hydrocarbylsulphonyloxy group (e.g. methanesulphonyloxy) such compounds may be prepared by reacting the compounds of formula (XIII) with methanesulphonyl chloride in the presence of a base (e.g. triethylamine). The reaction conveniently takes place in the presence of a solvent such as a halogenated hydrocarbon (e.g. dichloromethane) at a temperature ranging from 0-25°.

15 Compounds of formula (XIII) in which Y represents an oxygen or sulphur atom may be prepared by reacting a compound of formula (XIV) with a compound of formula (XV)



20 under conditions as described for the preparation of compounds of formula (X) above.

Compounds of formula (XIV) are either known compounds or may be prepared from the corresponding alcohols as described for the preparation of compounds of formula (III) above.

25 Compounds of formulae (XII) and (XV) are either known compounds or may be prepared by methods analogous to those used for the preparation of known compounds.

In addition, suitable methods for preparing intermediates of formulae (III), (IV), (IX), (XI), (XIII) and (XIV) are described in UK Patent Specifications Nos. 2140800A and 2159151A and in the exemplification included hereinafter.

30 In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired, such salts may be converted to the corresponding free bases using conventional methods.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting a compound of general formula (I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol, e.g. methanol, ethanol or isopropanol.

35 Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained by resolution of a corresponding racemate of a compound of general formula (I) using conventional methods.

40 Thus, in one example an appropriate optically active acid may be used to form salts with the racemate of a compound of general formula (I). The resulting mixture of isomeric salts may be separated for example by fractional crystallisation, into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

45 Specific diastereoisomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or by conversion of a mixture of isomers of a compound of general formula (I) into appropriate diastereoisomeric derivatives e.g. salts which then can be separated by conventional means e.g. by fractional crystallisation.

50 The following examples illustrate the invention. Temperatures are in °C. 'Dried' refers to drying using magnesium sulphate or sodium sulphate. Unless otherwise stated, thin layer chromatography (T.L.C.) was carried out on silica and flash column chromatography (F.C.C.) on silica (Merck 9385) using one of the following solvent systems: A - ethyl acetate:methanol:triethylamine, B - toluene:ethanol:0.88 ammonia, C - toluene:ethanol:triethylamine. The following abbreviations are used : DMF - dimethylformamide, TAB - tetra-n-butylammonium hydrogen sulphate, DEA - N,N-diisopropylethylamine.

2-[2-[(6-Bromohexyl)oxy]ethyl]naphthalene

2-Naphthaleneethanol (3g), 1,6-dibromoheptane (8ml), TAB (0.5g) and sodium hydroxide (8g) in 16 ml water) were stirred at room temperature under nitrogen for 26h. Water (80ml) was added and the mixture extracted with diethyl ether (3x100ml). The combined extracts were washed with water (80ml), brine (80ml), dried and evaporated to give a colourless oil (13g). The oil was purified by FCC eluting with cyclohexane (2:1) and then cyclohexane-ethyl acetate (40:1) to give the title compound, (4.23g), as a colourless oil, t.l.c. (cyclohexane-ethyl acetate; 5:1) Rf 0.45.

10

Intermediate 21-[2-[(6-Bromohexyl)oxy]ethyl]naphthalene

15

1-Naphthaleneethanol (3.00g) and 1,6-dibromohexane (12.73g) were treated according to the method of Intermediate 1. FCC eluting with cyclohexane followed by ethyl acetate-cyclohexane (1:20, then 1:4) gave the title compound (4.32g) as a colourless oil.

20

Analysis Found: C, 64.5; H, 6.65; Br, 23.75.
 $C_{16}H_{25}BrO$ requires C, 64.5; H, 6.9; Br, 23.85%.

25

Intermediate 3

30

1-[(5-Bromopentyl)oxy]methyl]naphthalene

1-Naphthalenemethanol (6.00g) and 1,5-dibromopentane (11.5ml) were treated according to the method of Intermediate 1. FCC eluting with ether-cyclohexane (1:49→2:48) gave the title compound as a colourless oil (8.41g), t.l.c. (Cyclohexane-ether 19:1) Rf 0.22;

35

Intermediate 4

40

7-[(1-Naphthalenyl)methoxy]-2-heptanone

1-[(5-Bromopentyl)oxy]methyl]naphthalene (9.96g) in dry ether (40ml) was added to magnesium turnings (0.94g) and iodine (one small crystal) under nitrogen with stirring at a rate which maintained a gentle reflux. The mixture was stirred at reflux for 30min, cooled to ambient temperature and added over 2.5h to acetic anhydride (7.67ml) in ether (15ml) at -78° under nitrogen with vigorous stirring. After 2h at -78°, the mixture was allowed to warm to -10° and treated with aqueous saturated ammonium chloride (50ml). Ether (50ml) was added, the aqueous layer was separated and the ethereal layer was washed with 1M-aqueous sodium hydroxide (100ml). The combined aqueous washings were extracted with ether (100ml) and this extract was combined with the ethereal layer above. The dried ethereal solution was evaporated and the residual oil purified FCC. Elution with ether-cyclohexane (1:4) gave, after Kugelrohr distillation, the title compound as a colourless oil (3.39g), b.p. 190°.0.3 Torr (Kugelrohr).

55

Intermediate 5N-[6-[[3-[6-Methoxy-2-naphthalenyl]-2-propynyl]oxy]hexyl]benzenemethanamine

Nitrogen was bubbled through a mixture of N-[6-[(2-propynyl)oxy]hexyl]benzenemethanamine (4.14g), 2-bromo-6-methoxynaphthalene (4.0g) and dicyclohexylamine (5.82g) in acetonitrile (60ml) for 15 min. Bis-(triphenylphosphine)palladium (II) chloride (120mg) and copper (I) iodide (10mg) were added and the mixture was stirred at reflux under nitrogen for 4h, cooled, diluted with ether (100ml), filtered and the filtrate was evaporated *in vacuo*. Purification by FCC eluting with System B (90:10:1) gave the title compound as a brown oil (1.18g), t.i.c. (System B 40:10:1) Rf 0.19.

Intermediate 6

10

(Z)-N-[5-[1-Hydroxy-2-[[6-[3-(6-methoxy-2-naphthalenyl)-2-propenyl]oxy]hexyl](phenylmethyl)amino]ethyl]-2-(phenylmethoxy)phenyl]methanesulphonamide

15 A solution of N-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]methanesulphonamide (0.96g), N-[6-[3-(6-methoxy-2-naphthalenyl)-2-propenyl]oxy]hexyl]benzenemethanamine (1.38g) and DEA (0.47g) in dichloromethane (22ml) was stirred at room temperature under nitrogen for 22h, diluted with water (100ml) and extracted with dichloromethane (2x100ml). The combined organic extracts were dried and evaporated *in vacuo* to give an oil. The oil was dissolved in methanol (20ml) and dichloromethane (20ml) and sodium borohydride (0.25g) were added portionwise to the solution at 0 °C under nitrogen. The solution was stirred at room temperature for 1h, cooled to 0 °C and a further portion of sodium borohydride (0.1g) added. The solution was stirred at room temperature for 30 min and then carefully diluted with water (10ml) and evaporated *in vacuo*. The residue was partitioned between dichloromethane (100ml) and water (100ml). The aqueous phase was re-extracted with dichloromethane (100ml) and the combined organic fractions dried and evaporated *in vacuo* to give an oil. Purification by FCC eluting with System C (100:2:1) gave the title compound as a colourless oil (0.77g), t.i.c. (System C 98:2:1) Rf 0.23.

Intermediate 7

30

4-Amino-3,5-dichloro- α [[[6-[3-(6-methoxy-2-naphthalenyl)-2-propynyl]oxy]hexyl](phenylmethyl)amino]-methyl]benzenemethanol

35 A solution of 1-(4-amino-3,5-dichloro)-2-bromoethanone (0.78g), N-[6-[3-(6-methoxy-2-naphthalenyl)-2-propynyl]oxy]hexyl]benzenemethanamine (1.1g) and DEA (0.39g) in tetrahydrofuran (25ml) was stirred under nitrogen for 20h. The mixture was filtered and the filtrate evaporated *in vacuo* to give an oil. The oil was dissolved in methanol (20ml) and dichloromethane (30ml) and sodium borohydride (0.28g) added portionwise to the solution at 0 °C under nitrogen. The solution was stirred at room temperature for 2h, cooled to 0 °C and a further portion of sodium borohydride (0.14g) added. The solution was then stirred at room temperature for 1h, carefully diluted with water (10ml) and evaporated *in vacuo*. The residue was partitioned between ethyl acetate (100ml), water (100ml), the aqueous phase was re-extracted with ethyl acetate (100ml) and the combined organic fractions dried and evaporated *in vacuo* to give an oil. Purification by FCC eluting with System C (100:1:1) gave the title compound as a colourless oil (1.18g), t.i.c. (System C 98:2:1) Rf 0.53.

Intermediate 8

50

4-[(2-Naphthalenyl)oxy]butanol

A mixture of 2-[(4-bromobutyl)oxy]naphthalene (5.5g), sodium acetate (13.1g), triethylpropylammonium chloride (1.21g) and water (19ml) was stirred at ca 100 °C for 2h, 2N sodium hydroxide solution (32ml) and ethanol (32ml) were added to the cooled mixture which was stirred for a further 10min at room temperature. The ethanol was evaporated *in vacuo* and the residue diluted with brine (150ml) and extracted with ether (2x100ml), which was dried and evaporated *in vacuo* to give a white solid. The solid was dissolved in ether and purified by FCC eluting with hexane-ether (2:1→1:2) to give the title compound as a

white solid (1.36g), m.p. 66.5-67.5°.

5 Intermediate 9

2-[4-[(6-Bromohexyl)oxy]butoxy]naphthalene

10 A mixture of 4-[(2-naphthalenyl)oxy]butanol (2.4g), 1,6-dibromohexane (5.3mL), TAB (1g) and 50% sodium hydroxide solution (24mL) was stirred at room temperature for 19h. The mixture was diluted with water (100mL) and extracted with ether (2x150mL). The combined organic fractions were dried and evaporated *in vacuo* to give an oil. Purification by FCC eluting with hexane followed by hexane-ether (19:1 → 8:1) gave the title compound as a colourless oil, (2.34g), t.l.c. (ether-hexane 1:1) Rf 0.85.

15

Intermediate 10

N-[6-[(2-Naphthalenyl)oxy]butoxy]hexylbenzenemethanamine

20 2-[4-[(6-Bromohexyl)oxy]butoxy]naphthalene (2.25g) and benzylamine (3.88g) were stirred under nitrogen at ca. 125° for 2h. The solution was diluted with 8% sodium bicarbonate (100mL) and extracted with diethyl ether (2x100mL), dried and evaporated *in vacuo* to give an oil. Purification by FCC eluting with System C (98:2:1) gave the title compound as a yellow oil (2.3g), t.l.c. (System C 40:10:1) Rf 0.71.

25

Intermediate 11

30 2-[(2-[(6-Bromohexyl)oxy]ethyl)thio]naphthalene

35 A mixture of 1,6-dibromohexane (9mL), 50% w/v sodium hydroxide (40mL), 2-(2-naphthalenyl)-thloethanol (4g), TAB (0.8g) and hexane (30mL) was stirred vigorously at 20°, under nitrogen for 4h. Water (100mL) and ether (100mL) were added and the mixture was further extracted with ether (100, 2x50mL). The combined, dried ether extracts were evaporated *in vacuo* to give a yellow oil. Purification by FCC eluting with light petroleum (b.p. 60-80°):ether (30:1→1:1) gave the title compound as a white crystalline solid (5.7g), m.p. 38-40° (softens 36°).

40

Example 1

4-Hydroxy- α^1 -[[[6-[2-(2-naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol

45 α^1 -(Aminomethyl)-4-hydroxy-1,3-benzenedimethanol (1.31g), 2-[2-[(6-bromohexyl)oxy]ethyl]naphthalene (2g) and DEA (0.83mL) in DMF (dried over type 4Å sieves, 20mL) were stirred at 100° under nitrogen for 2h. The cooled mixture was poured into aqueous saturated sodium bicarbonate (80mL) and extracted with ethyl acetate (3 x 100mL). The combined extracts were washed (water, 100mL), dried and evaporated to give a yellow tacky solid (3.5g). This solid was adsorbed onto silica (Merck 7734, 2g) from methanol and the resultant silica gel plug was applied to an FCC column. Elution with System A (89:10:1) gave a white solid (0.95g), which crystallised from ethyl acetate (20mL) to give the title compound (0.32g) as a white solid, m.p. 112-114°.

55

Analysis	Found:	C,	73.3;	H,	8.2;	N,	3.1.
C ₂₇ H ₃₅ NO ₄ .O.2H ₂ O	requires	C, C,	73.5;	H, H,	8.1;	N, N,	3.2%.

Water analysis, 0.2 mole water

Example 24-Hydroxy- α^1 -[[[6-[2-(1-naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol

5 A mixture of α^1 -(aminomethyl)-4-hydroxy-1,3-benzenedimethanol (0.75g), 1-[2-[(6-bromoethyl)oxy]-ethyl]naphthalene (1.00g), DEA (0.85mL) in DMF (6.5mL) was heated at 80° for 2h. The clear brown solution was diluted with water (65mL), acidified to pH4 with 2N hydrochloric acid and then basified to pH8 with solid potassium bicarbonate. The mixture was extracted with ethyl acetate (2x65mL) and the combined extracts were washed with water (65mL) and brine (30mL). The dried extracts were evaporated, the residue dissolved in ethyl acetate-methanol (1:1) and absorbed onto silica (Merck 7734, 5.00g). The silica gel plug was applied to an FCC column and elution with System A (90:10:1) gave the title compound (0.22g) as a white solid m.p. 105°-107°.

10

Analysis	Found:	C,	73.1;	H,	7.85;	N,	3.1.
C ₂₇ H ₃₅ NO ₄	requires	C,	73.1;	H,	8.1;	N,	3.1%.

Example 34-Hydroxy- α^1 -[[1-methyl-6-[[1-naphthalenyl)methyl]oxy]hexyl]amino]methyl]-1,3- benzenedimethanol

25 7-[(1-naphthalenyl)methoxy]-2-heptanone (1.00g) and α^1 -[[bis(phenylmethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol (1.34g) in ethanol (40mL) were hydrogenated over pre-reduced 10% palladium oxide-on-carbon (0.2g) and 5% platinum oxide-on-carbon (0.2g) at room temperature and pressure. The catalyst was removed (hyflo) and the solution evaporated. The residual oil was purified by FCC, eluting with System A (94:5:1) to give a white solid (704mg). The white solid was further purified by repeating the chromatography procedure to give the title compound as a white solid (469mg) m.p. 99-101°

30

Analysis	Found:	C,	73.7;	H,	8.5;	N,	3.15.
C ₂₇ H ₃₅ NO ₄	requires	C,	74.1;	H,	8.05;	N,	3.2%.

Example 4N-[2-Hydroxy-5-[1-hydroxy-2-[[6-[3-(6-methoxy-2-naphthalenyl)propoxy]hexyl]amino]ethyl]phenyl]-methanesulphonamide

45 A solution of Z-N-[5-[1-hydroxy-2-[6-[3-(6-methoxy-2-naphthalenyl)-2-propenyl]hexyl](phenylmethyl)-amino]methyl]benzenemethanol (0.73g) in absolute ethanol (30mL) was hydrogenated over pre-reduced 10% palladium on charcoal catalyst (0.4g) in absolute ethanol (10mL). The mixture was filtered through hyflo and evaporated *in vacuo*. The resultant solid was dissolved in dichloromethane (50mL) and washed with 8% sodium bicarbonate (50mL). The aqueous phase was re-extracted with dichloromethane (50mL) and the combined organic extracts dried and evaporated *in vacuo* to give a solid. Trituration with diethyl ether gave the title compound as an off-white solid (0.25g), m.p. 87-89°.

50

Analysis	Found:	C,	63.2;	H,	7.1;	N,	5.1.
C ₂₉ H ₄₀ N ₂ O ₅ S.0.25H ₂ O	requires	C,	63.4;	H,	7.4;	N,	5.1%.

Example 5Amino-3,5-dichloro- α -[[6-[3-(6-methoxy-2-naphthalenyl)propoxy]hexyl]amino]methyl]benzenemethanol

5 A solution of 4-amino-3,5-dichloro- α -[[6-[3-(6-methoxy-2-naphthalenyl)-2-propynyl]oxy]hexyl]-
(phenyl)methyl]amino]methyl]benzenemethanol (1.11g) in absolute ethanol (50ml) was hydrogenated over
pre-reduced 10% palladium on charcoal catalyst (0.4g) in absolute ethanol (10ml) containing hydrochloric
acid (1:9 conc. hydrochloric acid/ethanol, 1.67ml). The mixture was filtered through hyflo and evaporated in
10 vacuo to give an oil. The oil was partitioned between dichloromethane (150ml) and 8% sodium bicarbonate
(100ml). The aqueous phase was re-extracted with dichloromethane (100ml) and the combined organic
extracts dried and evaporated in vacuo to give an oil. Purification by FCC eluting with System C (95:5:1) to
give the title compound as a white solid (513mg), m.p. 102.5 - 103.5°.

15

Analysis	Found:	C, 64.5;	H, 7.5;	N, 5.3;	Cl, 13.9.
$C_{28}H_{35}Cl_2N_2O_3$	requires	C, 64.7;	H, 7.0;	N, 5.4;	Cl, 13.8%

Example 65-[1-Hydroxy-2-[[6-[2-naphthalenyl]ethoxy]hexyl]amino]ethyl]-1,3-benzenediol,4,4'-methylenebis[3-hydroxy-
2-naphthalenecarboxylate] (2:1) salt.

25 A mixture of 5-(2-amino-1-hydroxyethyl)-1,3-benzenediol (1.02g), 2-[3-(6-bromohexyl)oxyethyl]-
naphthalene (1.34g) and DEA (1.74ml) in DMF (25ml) was heated at 100° for 3h under nitrogen. The
solvent was removed in vacuo and the residue purified by FCC eluting with System B (80:20:1) to give the
base as a solid pink glass (0.8g).

A mixture of the base (0.4g) and 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (0.18g) in
methanol (30ml) was heated under reflux for 30min. The methanol was removed in vacuo and the residue
triturated under ether (20ml) to give the title compound as an off-white solid (0.52g), m.p. 105-110°
(softens 100°).

35

Analysis	Found:	C, 70.2;	H, 6.9;	N, 2.1.
$(C_{26}H_{33}NO_4)_2 C_2H_6O_6 \cdot 2.5H_2O$	requires	C, 70.35;	H, 6.85;	N, 2.2%.

40

Example 7N-[2-Hydroxy-5-[1-hydroxy-2-[[6-[4-[(2-naphthalenyl)oxy]butoxy]hexyl]amino]ethyl]phenyl]-
methanesulphonamide

45 A solution of N-[5-(bromoacetyl)-2-(phenylmethoxy)phenyl]methanesulphonamide (1.96g), N-[6-14-[(2-
naphthalenyl)oxy]butoxy]hexyl]benzenemethanamine (2.0g) and DEA (0.96g) in dichloromethane (45ml)
50 was stirred under nitrogen at room temperature for 22h. The mixture was treated with water (100ml) and
extracted with dichloromethane (2x150ml). The combined organic extracts were dried and evaporated in
vacuo to give an oil which was dissolved in methanol (30ml) and dichloromethane (20ml) and cooled to 0-
5° C under nitrogen. Sodium borohydride (0.50g) was added portionwise and the solution stirred at room
temperature for 30min, then carefully diluted with water (20ml). The solvent was evaporated in vacuo, the
55 residue partitioned between water (100ml) and dichloromethane (150ml) and the aqueous phase re-
extracted with dichloromethane (150ml), the combined organic extracts being dried and evaporated in
vacuo to give an oil which was purified by FCC eluting with System C (95:5:1). A solution of the oil (3.41g)
in absolute ethanol (60ml) was hydrogenated over pre-reduced 10% palladium on charcoal catalyst (50%

aqueous paste, 1.5g) in absolute ethanol (10mL) for 4.5h. The mixture was filtered through hyflo and evaporated *in vacuo* to give an oil which was purified by FCC eluting with System B (40:10:1) to give a cream solid. Trituration with diethyl ether gave the title compound as a white solid (1.23g), m.p. 99.5-100.5°.

5

Analysis	Found:	C, 64.1;	H, 7.3;	N, 5.2.
C ₂₃ H ₄₀ N ₂ O ₆ S	requires	C, 63.9;	H, 7.4;	N, 5.1%.

10

Example 8

15 N-[2-Hydroxy-5-[1-hydroxy-2-[[6-[4-[(2-naphthalenyl)oxy]butoxy]hexyl]amino]ethyl]phenyl]-methanesulphonamide, 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylate] salt (2:1)

A solution of N-[2-hydroxy-5-[2-hydroxy-2-[[6-[4-[(2-naphthalenyl)oxy]butoxy]hexyl]amino]ethyl]phenyl]-methanesulphonamide (449mg) in methanol (17mL) and 4,4'-methylenebis[3-hydroxy-2-naphthalenecarboxylic acid] (160mg), was heated at reflux for 1h, cooled, filtered and the filtrate evaporated *in vacuo*. The solvent was triturated with dry ether to afford the title compound as an off-white foam (413mg), m.p. 100-106°.

25

Assay	Found:	C, 65.0;	H, 6.6;	N, 3.7;	S, 4.2.
C ₂₃ H ₄₀ N ₂ O ₆ S.0.5C ₂₃ H ₁₆ O ₆ .0.5H ₂ O	requires	C, 65.0;	H, 6.6;	N, 3.75;	S, 4.3%.

30

Example 9

4-Hydroxy- α' -[[[6-[2-[(2-naphthalenyl)thio]ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol

35 A solution of α' -(aminomethyl)-4-hydroxy-1,3-benzenedimethanol (1.0g), 2-[[2-[(6-bromohexyl)oxy]ethyl]thio]naphthalene (1.01g) and DEA (0.52g) in dry DMF (30mL) was stirred at 100° under nitrogen for 4h. The solvent was evaporated and the residue purified by FCC eluting with System B (39:10:1) to give a pale brown solid (0.76g). Trituration under ether (2x50mL) gave the title compound as a cream colored solid (0.39g.), m.p. 101-2°.

40

Analysis	Found:	C, 68.9;	H, 7.6;	N, 3.0;	S, 6.6.
C ₂₇ H ₄₅ NO ₄ S	requires	C, 69.05;	H, 7.5;	N, 3.0;	S, 6.8%.

45

The following are examples of suitable formulations of compounds of the invention. The term 'active ingredient' is used herein to represent a compound of the invention.

50

Tablets (Direct Compression)	
	mg/tablet
Active ingredient	2.0
Microcrystalline cellulose USP	196.5
Magnesium Stearate BP	1.5
Compression weight	200.0

55

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using 7mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to microcrystalline cellulose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film forming materials, such as hydroxypropylmethylcellulose, using standard techniques. Alternatively, the tablets may be sugar coated.

5

Metered Dose Pressurised Aerosol (Suspension Aerosol)		
	mg/metered dose	Per can
10	Active ingredient micronised Oleic Acid BP	0.100 26.40mg
	Trichlorofluoromethane BP	0.100 2.64mg
	Dichlorodifluoromethane BP	23.64 5.67g
		61.25 14.70g

15

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10-15 °C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves delivering 85mg of suspension are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

25

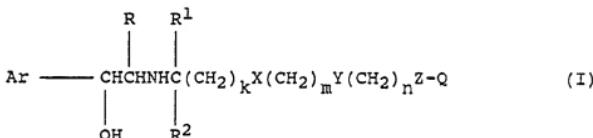
Inhalation Cartridges	
	mg/cartridge
	Active ingredient micronised Lactose BP to
	0.200 25.0

30 The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents in the cartridges are administered using a power inhaler such as the Glaxo Rotahaler.

35 Claims

1. Compounds of the general formula (I)

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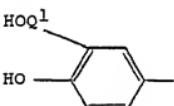
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and physiologically acceptable salts and solvates thereof, wherein
Ar represents the group

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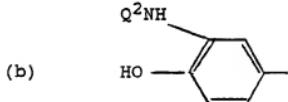
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(a)



and Q¹ represents a straight or branched C₁-alkylene group,

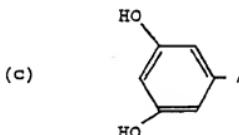
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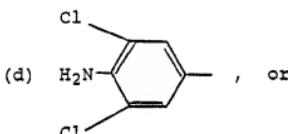
where Q² represents a group R³CO-, R³NHCO-, R³R⁴NSO₂- or R⁵SO₂-, where R³ and R⁴ each represent a hydrogen atom or a C₁-alkyl group, and R⁵ represents a C₁-alkyl group,

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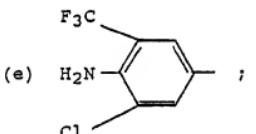


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R represents a hydrogen atom or a C₁-alkyl group;

R¹ and R² each independently represent a hydrogen atom or a methyl or ethyl group; and

k represents an integer from 1 to 8;

m represents zero or an integer from 2 to 7; and;

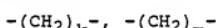
n represents an integer from 1 to 7 with the proviso that the sum total of k, m and n is 4 to 12;

X represents an oxygen or sulphur atom, and;

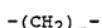
Y and Z each represent a bond, or an oxygen or sulphur atom with the proviso that when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7, or when Y and Z each independently represent an oxygen or sulphur atom then n is an integer from 2 to 7;

Q represents a naphthalenyl group which may optionally be substituted by one or two groups selected from C₁-alkyl, C₁-alkoxy, hydroxy and halogen.

45 2. Compounds as claimed in Claim 1 in which the sum total of carbon atoms in the chains



50 and



55

is 6, 7, 8, 9, 10 or 11.

3. Compounds as claimed in Claim 1 or 2 in which X is an oxygen atom, Y is a bond and Z is a bond or X is an oxygen atom, Y is a bond and Z is an oxygen or sulphur atom.

4. Compounds as claimed in any of Claims 1 to 3 in which R represents a hydrogen atom.

5. Compounds as claimed in any of Claims 1 to 4 in which R¹ is a hydrogen atom and R² is a hydrogen atom or a C₁-alkyl group or R¹ is a methyl group and R² is a methyl group.

6. Compounds as claimed in any of Claims 1 to 5 in which Q is an unsubstituted naphthalenyl moiety attached to the remainder of the molecule at the 1- or 2- position or Q is a naphthalenyl moiety substituted by a single methoxy group.

7. Compounds as claimed in Claim 1 in which

Ar represents group (a) wherein Q¹ represents -CH₂-; or group (b) wherein Q² represents CH₃SO₂-; or group (c) or group (d);

10 R represents a hydrogen atom;

R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom;

X represents an oxygen atom;

Y represents a bond;

15 Z represents a bond or an oxygen or sulphur atom; and

k is 5, m is zero and n is an integer from 1 to 4.

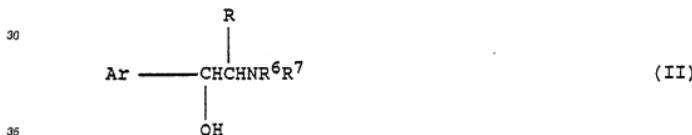
8. 4-Hydroxy- α^1 -[[6-[2-(2-naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol; 4-amino-3,5-dichloro- α^1 -[[6-[3-(6-methoxy-2-naphthalenyl)propoxy]hexyl]amino]methyl]benzenemethanol, 5-[1-hydroxy-2-[[6-[2-(2-naphthalenyl)ethoxy]hexyl]amino]ethyl]-1,3-benzenediol;

20 N-[2-hydroxy-5-[1-hydroxy-2-[[6-[4-[2-(2-naphthalenyl)oxy]butoxy]hexyl]amino]ethyl]phenyl]-methanesulphonamide;

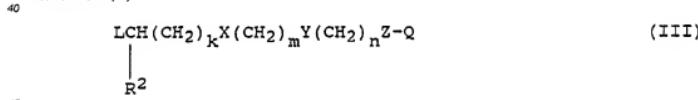
4-hydroxy- α^1 -[[6-[2-(1-naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol; and physiologically acceptable salts and solvates thereof.

9. A process for the preparation of compounds as claimed in any of Claims 1 to 8 or a physiologically acceptable salt or solvate thereof which comprises:

25 (1a) for the preparation of a compound of formula (I) in which R¹ is a hydrogen atom, alkylating an amine of general formula (II)

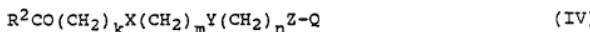


in which R⁶ is a hydrogen atom or a protecting group and R⁷ is a hydrogen atom, with an alkylating agent of formula (III)



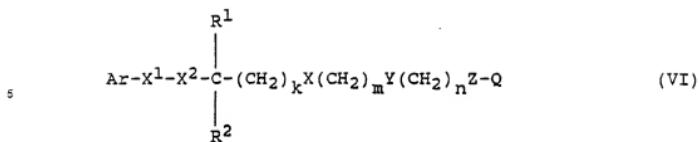
in which L is a leaving group, followed, if necessary, by removal of any protecting group present; or

(1b) for the preparation of a compound of formula (I) in which R¹ is a hydrogen atom, alkylating an amine of general formula (II) as defined above except that R⁷ is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (IV)

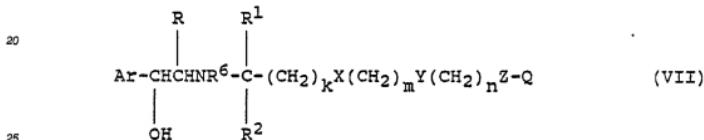


55 in the presence of a reducing agent, followed, if necessary, by removal of any protecting group present; or

(2) reducing an intermediate of general formula (VI)



10 in which
 X^1 is $-\text{CH}(\text{OH})-$ or a group convertible thereto by reduction;
 X^2 is $-\text{CHRN}^6-$, where R^6 represents a hydrogen atom or a protecting group, or a group convertible thereto by reduction;
15 at least one of X^1 and X^2 representing a reducible group, followed, if necessary, by removal of any protecting group present; or
(3) deprotecting a protected intermediate of general formula (VII)

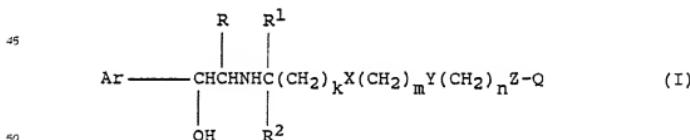


in which R^6 is a protecting group and/or at least one of the hydroxy group(s) in Ar is protected and/or the group Q contains a protecting group;
30 and when the compound of formula (I) is obtained as a mixture of enantiomers optionally resolving the mixture to obtain the desired enantiomer;
and/or, if desired, converting the resulting compounds of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

35 10. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in any of Claims 1 to 8 or a physiologically acceptable salt or solvate thereof, together with at least one physiologically acceptable carrier or excipient.

40 Claims for the following Contracting States: ES, GR

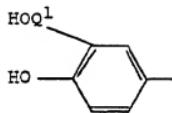
1. A process for the preparation of compounds of the general formula (I)



and physiologically acceptable salts and solvates thereof, wherein
Ar represents the group

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(a)

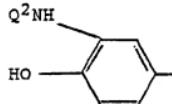


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where Q¹ represents a straight or branched C₁-3alkylene group,

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(b)

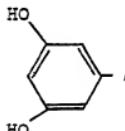


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where Q² represents a group R³CO-, R³R⁴NHCO-, R³R⁴NSO₂- or R⁵SO₂-, where R³ and R⁴ each represent a hydrogen atom or a C₁-3alkyl group, and R⁵ represents a C₁-3alkyl group,

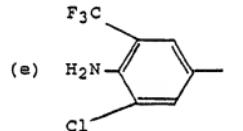
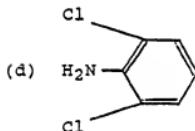
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(c)



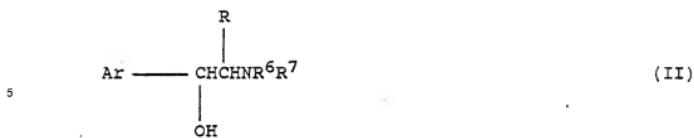
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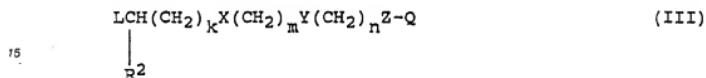


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R represents a hydrogen atom or a C₁-3alkyl group;
 R¹ and R² each independently represent a hydrogen atom or a methyl or ethyl group; and
 k represents an integer from 1 to 8;
 m represents zero or an integer from 2 to 7; and;
 n represents an integer from 1 to 7 with the proviso that the sum total of k, m and n is 4 to 12;
 X represents an oxygen or sulphur atom, and;
 Y and Z each represent a bond, or an oxygen or sulphur atom with the proviso that when Y is a bond m is zero, or when Y represents an oxygen or sulphur atom m is an integer from 2 to 7, or when Y and Z each independently represent an oxygen or sulphur atom then n is an integer from 2 to 7;
 Q represents a naphthalenyl group which may optionally be substituted by one or two groups selected from C₁-3alkyl, C₁-3alkoxy, hydroxy and halogen,
 which comprises:
 (1a) for the preparation of a compound of formula (I) in which R¹ is a hydrogen atom, alkylating an
 56 amine of general formula (II)

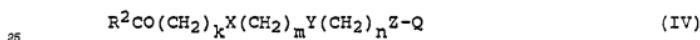


10 in which R^6 is a hydrogen atom or a protecting group and R^7 is a hydrogen atom, with an alkylating agent of formula (III)



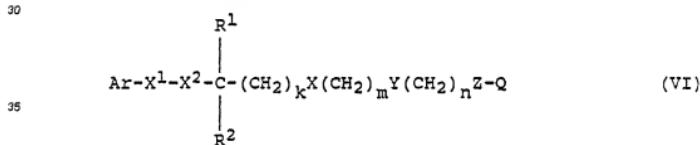
in which L is a leaving group, followed, if necessary, by removal of any protecting group present; or

20 (1b) for the preparation of a compound of formula (I) in which R^1 is a hydrogen atom, alkylating an amine of general formula (II) as defined above except that R^7 is a hydrogen atom or a group convertible thereto under the reaction conditions, with a compound of general formula (IV)



in the presence of a reducing agent, followed, if necessary, by removal of any protecting group present; or

(2) reducing an intermediate of general formula (VI)



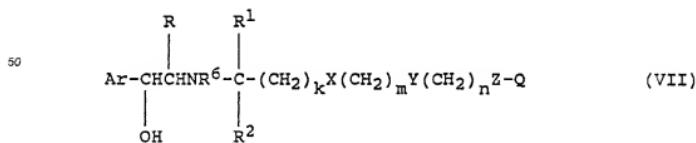
40 in which

X^1 is $-\text{CH}(\text{OH})-$ or a group convertible thereto by reduction;

X^2 is $-\text{CHNR}^6-$, where R^6 represents a hydrogen atom or a protecting group, or a group convertible thereto by reduction;

45 at least one of X^1 and X^2 representing a reducible group, followed, if necessary, by removal of any protecting group present; or

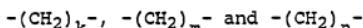
(3) deprotecting a protected intermediate of general formula (VII)



in which R^6 is a protecting group and/or at least one of the hydroxy group(s) in Ar is protected and/or the group Q contains a protecting group;

and when the compound of formula (I) is obtained as a mixture of enantiomers optionally resolving the mixture to obtain the desired enantiomer;
and/or, if desired, converting the resulting compounds of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

5 2. A process as claimed in Claim 1 for the preparation of compounds in which the sum total of carbon atoms in the chains



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is 6, 7, 8, 9, 10 or 11.

15 3. A process as claimed in Claim 1 or 2 for the preparation of compounds in which X is an oxygen atom, Y is a bond and Z is a bond or X is an oxygen atom, Y is a bond and Z is an oxygen or sulphur atom.

4. A process as claimed in any of Claims 1 to 3 for the preparation of compounds in which R represents a hydrogen atom.

20 5. A process as claimed in any of Claims 1 to 4 for the preparation of compounds in which R¹ is a hydrogen atom and R² is a hydrogen atom or a C₁-alkyl group or R¹ is a methyl group and R² is a methyl group.

6. A process as claimed in any of Claims 1 to 5 for the preparation of compounds in which Q is an unsubstituted naphthalenyl moiety attached to the remainder of the molecule at the 1- or 2- position or Q is a naphthalenyl moiety substituted by a single methoxy group.

25 7. A process as claimed in Claim 1 for the preparation of compounds in which R represents group (a) wherein Q¹ represents -CH₂-, or group (b) wherein Q² represents CH₃SO₂-, or group (c) or group (d);

R represents a hydrogen atom;

R¹ represents a hydrogen atom or a methyl group;

R² represents a hydrogen atom;

30 X represents an oxygen atom;

Y represents a bond;

Z represents a bond or an oxygen or sulphur atom; and

k is 5, m is zero and n is an integer from 1 to 4.

35 8. A process as claimed in claim 1 for the preparation of a compound selected from:
4-hydroxy- α^1 -[[[6-[2-(2-naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol;
4-amino-3,5-dichloro- α^1 -[[[6-[3-(6-methoxy-2-naphthalenyl)propoxy]hexyl]amino]methyl]-benzenemethanol,
5-[1-hydroxy-2-[[6-[2-naphthalenyl]ethoxy]hexyl]amino]ethyl]-1,3-benzenediol;
N-[2-hydroxy-5-[1-hydroxy-2-[[6-[4-(2-naphthalenyl)oxy]butoxy]hexyl]amino]ethyl]phenyl]-methanesulphonamide;

40 4-hydroxy- α^1 -[[[6-[2-(1-naphthalenyl)ethoxy]hexyl]amino]methyl]-1,3-benzenedimethanol;
and physiologically acceptable salts and solvates thereof.

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